REMARKS

I. Status of Claims:

Claims 1-4, 9, 12, and 14-26 were pending in this application[1].

Claims 3 and 14 have been canceled without prejudice.

Claims 1, 4, 9, 12, and 22 have been amended and claims 27-30 have been newly added. Support for the claim amendments and the new claims can be found, for example, in the original claims, page 5, lines 16-20, the paragraph bridging pages 6-7, page 9, lines 3-8, and Example 1 at pages 18-19 of the application as filed. Accordingly, no new matter has been added.

Upon entry of this Amendment, claims 1-2, 4, 9, 12, and 15-30 will be pending in this application.

II. Withdrawn Rejections:

Applicants acknowledge that the Examiner has withdrawn the following rejections:

(i) rejection of claims 1-7 under 35 U.S.C. § 102(b) as being anticipated by Hansen (Hansen *et al.*, *Proc. Nat. Acad. Sci. USA*, 98(22):12659-12664 (2001));

(ii) rejection of claims 10 and 11 under 35 U.S.C. § 102(b) as being anticipated by Punt (Punt *et al.*, *Cancer Immunol. Immunother.*, 38:225-232 (1994)); and

(iii) rejection of claims 1-13 under 35 U.S.C. § 103(a) as being unpatentable over Hansen in view of Larrick (Larrick *et al.*, *Immunol. Rev.* 130: 69-85 (1992)) (*see,* Final Action, page 2, sections 2-4).

III. Information Disclosure Statements:

Applicants thank the Examiner for consideration of the references submitted with the Information Disclosure Statement filed June 26, 2007.

Applicants are submitting a new Information Disclosure Statement with this Amendment. Applicants respectfully request that the PTO-Form 1449 be initialed and returned with the next Action.

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[1] The Action lists claims 1-4, 9, and 12-26 as pending, and states that "[c]laims 5-8 and 10-11 were cancelled" (see, Final Action, page 2, section 1). Applicants note that claims 5-8, 10-11, and 13 were previously cancelled. Thus, upon entry of the last filed amendment (*i.e.,* the Amendment filed December 4, 2007), claims 1-4, 9, 12, and 14-26 were pending in this application.

IV. Claim Objection:

Claim 22 was objected to because "arteriosclerotic" was misspelled as "ateriosclerotic" (*see*, Final Action, page 3, section 5).

Claim 22 has been amended to correct the spelling of this term. Applicants thank the Examiner for pointing out the error, and submit that the grounds for this objection have been overcome.

V. Rejections Under 35 U.S.C. § 112, First Paragraph, Written Description:

Claims 15 and 16 were rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the written description requirement. Specifically, the Action alleges that the amendment adding claims 15 and 16 introduces new matter (*see,* Final Action, page 3, section 6).

Applicants respectfully submit that claims 15 and 16 do not introduce new matter. Claim 15 is dependent on claim 1 and requires that the method of claim 1 be repeated for twenty or fewer B cells. Claim 16 is also dependent on claim 1 and requires that the method of claim 1 be repeated for five or fewer B cells. The application teaches that the number of B cells to be isolated is not limited, and discloses as examples, 1-100 cells, 1-50 cells, 20 cells or less, 5 cells or less, or a single cell (*see,* page 6, lines 31-33). In the paragraph immediately following this disclosure, the application teaches that "if an antibody gene obtained from a single cell is used, repeated cloning of the gene would be required when comparing multiple antibodies with different reactivities. Comparison of multiple antibodies is useful for obtaining a suitable antibody with purpose-oriented characteristics" (*see,* page 7, lines 3-6). In addition, Applicants draw the Examiner's attention to Example 1, in which the method of claim 1 was repeated at least seven times (*see,* Figs. 1, 5, 7, 9, 11, 13, and 15). When the teachings of both these paragraphs are understood in context by one of ordinary skill in the art, Applicants aver that the ordinary skilled artisan would conclude that Applicants were in possession of the subject matter of claims 15 and 16 and that these claims do not introduce new matter. Specifically, the ordinary skilled artisan after reading both paragraphs would appreciate that the method of claim 1 could be repeated for any of the numbers of cells listed in the application, including for twenty or fewer B cells or for five or fewer B cells.

Because claims 15 and 16 are fully supported by the application as filed, these claims do not introduce any new matter. Accordingly, Applicants respectfully request that this rejection be reconsidered and withdrawn.

VI. Rejections Under 35 U.S.C. § 102:

Claims 1-4, 17, 20, 21, and 23 were rejected under 35 U.S.C. § 102(b) as purportedly being anticipated by Coronella (Coronella *et al.*, *Cancer Research*, 61:7889-7899 (2001)) as evidenced by Webster's New World Medical Dictionary (*see,* Final Action, page 3, section 7).

To anticipate a claim, a reference must teach each and every element of the claim (*see*, MPEP § 2131). Amended claim 1 recites, in relevant part, "isolating a single lesional tissue-infiltrating B cell from a lesional tissue by a technique that comprises using laser microdissection (LMD) to excise a region comprising the B cell from a section of the lesional tissue." Coronella fails to teach this method, as acknowledged by the Office at page 6 of the Final Action (*see,* second full paragraph).

Because Coronella fails to teach each and every element of Applicants' claimed invention, Coronella does not anticipate amended claim 1 or the claims depending from claim 1 (*i.e.,* claims 2-4, 17, 20, 21, and 23).

VII. Rejections Under 35 U.S.C. § 103:

(a) Claims 1-4, 14, 17-21, and 23 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Coronella as evidenced by Webster's New World™ Medical Dictionary, in view of Obiakor (Obiakor *et al., Analytical Biochemistry*, 306:55-62 (2002)) (*see,* Final Action, pages 5-6, section 8).

To establish a *prima facie* case of obviousness the Patent Office must identify a reason that would have prompted a person of ordinary skill in the relevant field to modify the prior art to operate as the claimed invention does (*see,* MPEP § 2143). In addition, there must be a reasonable expectation of success found in the art. "To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight

syndrome wherein that which only the inventor taught is used against its teacher." *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1553 (Fed. Cir. 1983).

Amended claim 1 is directed to a method for isolating a polynucleotide encoding an antibody against a lesional tissue, comprising isolating a single lesional tissue-infiltrating B cell from a lesional tissue, *wherein the step of isolating the lesional tissue-infiltrating B cell comprises excising a region comprising the B cell from a section of the lesional tissue by laser microdissection (LMD)*; and obtaining a polynucleotide encoding an antibody heavy chain and a polynucleotide encoding an antibody light chain of the isolated B cell.

Coronella is directed to determining if the lymphoplasmacytic infiltrates in breast cancer tissue represent a tumor-specific humoral immune response as opposed to a non-specific cytokine-driven response (*see,* Coronella, Abstract; first paragraph of Results at page 7891; and first paragraph of Discussion at page 7897). To make this determination, Coronella relies on antibody sequences both from pooled sequences in combinatorial libraries and from single cell sampling of the tumor (*see,* Coronella, page 7890, left column, first full paragraph; and page 7895, left column, second and third full paragraphs). Coronella's single cell analysis comprises manually disaggregating cells of the tumor, purifying lymphoplasma cells by Ficoll gradient centrifugation, isolating $CD38^{hi}$ plasma cells from the lymphoplasma cells, sorting the isolated $CD38^{hi}$ plasma cells into single cell suspensions, and subjecting the isolated cells to PCR with V family primers and constant region primers (*see*, Coronella, page 7890, left column, first paragraph of "Tumors and Cells" and page 7890, right column, paragraph entitled "Single cells").

Obiakor teaches the use of laser capture microdissection (LCM) to study VDJ sequence diversification in rabbit appendix and splenic germinal centers.

Applicants respectfully submit that, without the benefit of Applicants' disclosure, one of ordinary skill in the art would not consider modifying Coronella with Obiakor as suggested in the Action for the reasons articulated below.

Applicants aver that one of ordinary skill in the art would not consider modifying Coronella with Obiakor because doing so would render Coronella's prior art method unsatisfactory for its intended purpose. Specifically, the combination would make it impossible for Coronella to preselect for $CD38^{+}$ cells. Plasma cells of all differentiation stages are identified

by the expression of high levels of the CD38 antigen. Thus, the CD38 pre-selection is necessary for Coronella to separate plasma cells from other mononuclear cells and tumor cells. It is this isolation followed by single cell sorting that enables Coronella to obtain the single plasma cells for RT-PCR analysis. Coronella needed the single cell plasma cells to isolate the sequences of native VH-VL pairs so as to use these sequences in combination with traditional molecular and biochemical methods for retrieving the eliciting antigen(s) in medullary ductal carcinoma (*see,* page 7894, right column, full paragraph and the paragraph bridging pages 7894-7895). If one were to utilize Obiakor's LCM method to attempt to obtain single plasma cells present in medullary ductal carcinoma, it would not be possible to perform the CD38 preselection. There is simply no reasonable expectation of success that the modified procedure would allow the ordinary artisan to isolate the single plasma cells desired by Coronella.

In addition, Coronella teaches that the single cell ("SC") technique actually employed by Coronella permits an unbiased sampling of plasma cells from the tumor, which was critical to at least some of the conclusions drawn in this reference: "Because the SC library is **an unbiased sampling** of this tumor, this 71% fraction (52-86%; 95% confidence interval) estimates the proportion of the total antibody response that is IgG1 and implies that this isotype is a fair sample of the total response that is present." (*see,* page 7895, left column, second full paragraph; emphasis supplied). In contrast, the LCM technique involves an inherent bias because it requires the individual carrying out the technique to visually select each of the B cells that is to be isolated from a tissue. There is no reasonable expectation that such a deliberate, one-at-a-time selection can be done in a way that does not involve at least an unconscious bias: e.g., one would expect that larger or more brightly stained B cells will be noticed and selected in preference to less noticeable ones.

Furthermore, Applicants respectfully aver that there would be no reason why one of ordinary skill in the art would replace the Ficoll gradient centrifugation/CD38 sorting procedure of Coronella with the tedious LCM procedure of Obiakor. While Obiakor does teach advantages of LCM over an alternative procedure, hydraulic micromanipulation (HM), both LCM and HM are tedious procedures for single cell isolation (*see,* page 56, Table 2 of Obiakor). The fact that Obiakor found LCM to be more efficient than HM merely suggests that as between these two procedures, LCM may be preferable. Importantly, Obiakor does not compare the LCM

technique with Coronella's Ficoll gradient centrifugation/CD38 sorting, which allows the preparation of unlimited numbers of CD58-expressing plasma cells and their rapid separation into wells of a 96-well PCR plate plasma cells for analysis. One of ordinary skill would have no reason to modify the straightforward and apparently easy technique described in Coronella with that described in Obiakor.

Finally, Applicants are unclear why claim 23 has been included in this rejection. Applicants do not see any connection between the disclosure in Coronella and the subject matter of claim 23.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of this rejection of claims 1-4, 14, 17-21, and 23 under 35 U.S.C. § 103(a)

(b) Claims 1-4, 9, 12, 17, 20, 21 and 23 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Coronella as evidenced by Webster's New World™ Medical Dictionary, in view of Larrick (Larrick *et al.*, *Immunological Reviews*, 130:69-85 (1992)) (*see,* Final Action, pages 6-7, section 9).

As a preliminary matter, Applicants are unclear why claim 23 has been included in this rejection. Applicants do not see any connection between the disclosure in Coronella and the subject matter of claim 23.

To establish a *prima facie* case of obviousness, all claim limitations must be taught or suggested by the prior art (*see*, MPEP § 2143.03). Each of the independent claims (*i.e.,* claims 1 and 9) has been amended to recite, in relevant part: "isolating a single lesional tissue-infiltrating B cell from a lesional tissue by a technique that comprises using laser microdissection (LMD) to excise a region comprising the B cell from a section of the lesional tissue." The teachings of Coronella and Larrick do not render obvious amended independent claims 1 and 9, or the claims depending from them, because neither reference, alone or in combination, teaches or suggests this step. Because the combined teachings of Coronella and Larrick do not teach or suggest all claim limitations, these references do not support an obviousness rejection of claims 1-4, 9, 12, 17, 20, 21 and 23.

(c) Claims 1-4, 9, 12, 14, 17-21 and 23 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Coronella as evidenced by Webster's New World™ Medical Dictionary, in view of Obiakor, and further in view of Larrick (*see,* Final Action, pages 7-8, section 10).

Applicants have explained in section (a) above why the combined teachings of Coronella and Obiakor fail to render obvious Applicants' claimed invention. The inclusion of Larrick's teachings to the combined teachings of Coronella and Obiakor fails to remedy the deficiencies of Coronella and Obiakor. Specifically, Larrick does not teach or suggest "isolating a single lesional tissue-infiltrating B cell from a lesional tissue by a technique that comprises using laser microdissection (LMD) to excise a region comprising the B cell from a section of the lesional tissue." Because the combined teachings of Coronella, Obiakor, and Larrick do not teach or suggest all claim limitations, these references do not support an obviousness rejection of claims 1-4, 9, 12, 14, 17-21 and 23.

(d) Claims 1-4, 14, 17-23, and 25 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Coronella as evidenced by Webster's New World™ Medical Dictionary, in view of Obiakor, and further in view of Koch (Koch *et al.*, *American Journal of Pathology*, 137(5):1199-1213 (1990)) (see, Final Action, pages 8-9, section 11).

Applicants have explained in section (a) above why the combined teachings of Coronella and Obiakor fail to render obvious Applicants' claimed invention. The inclusion of Koch's teachings to the combined teachings of Coronella and Obiakor fails to remedy the deficiencies of Coronella and Obiakor. Specifically, Koch does not teach or suggest "isolating a single lesional tissue-infiltrating B cell from a lesional tissue by a technique that comprises using laser microdissection (LMD) to excise a region comprising the B cell from a section of the lesional tissue." Applicants also note that Coronella's purpose of finding evidence of an antigen-derived humoral response in medullary ductal cancer has nothing to do with Koch's study regarding aortic aneurysms. Thus, there would simply be no reason why an ordinary artisan would consider combining the teachings of these references. Taken together, the combined teachings of Coronella, Obiakor, and Koch do not teach or suggest all claim limitations, so these references do not support an obviousness rejection of claims 1-4, 14, 17-23, and 25.

(e) Claims 1-4, 14, 17-21, 23, 24, and 26 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Coronella as evidenced by Webster's New World™ Medical Dictionary, in view of Obiakor, and further in view of Mallison (Mallison *et al.*, *Infection and Immunity*, 59(11):4019-4025 (1991)) (see, Final Action, pages 9-10, section 11).

Applicants have explained in section (a) above why the combined teachings of Coronella and Obiakor fail to render obvious Applicants' claimed invention. The addition of Mallison's teachings to the combined teachings of Coronella and Obiakor fails to remedy the deficiencies of Coronella and Obiakor. Specifically, Mallison does not teach or suggest "isolating a single lesional tissue-infiltrating B cell from a lesional tissue by a technique that comprises using laser microdissection (LMD) to excise a region comprising the B cell from a section of the lesional tissue." Applicants also note that Coronella's aim of finding evidence of an antigen-derived humoral response in medullary ductal cancer has nothing to do with Mallison's experiments regarding identifying which factors contribute to local accumulation of antibody forming cells in periodontal disease. These experiments are in no way directed to discovering antigens involved in periodontal disease; this reference uses a well known antigen – horseradish peroxidase (HRP) – in their chronic inflammation model (*see,* page 4020, left column, Induction Inflammation). Notwithstanding the above, even after combining the references cited in the Action, one would not be able "to discover the relevant antigens that may play a role in periodontal disease and its associated inflammation," as suggested by the Action, because the experiments are not done using periodontal lesions. Rather, the experiments use multiple inflammatory sites on the back of HRP-immune rabbits (*see,* page 4020, left column, Induction Inflammation). Thus, in the absence of hindsight reasoning, Applicants submit that there would simply be no reason why an ordinary artisan would consider combining the teachings of these references. Because the combined teachings of Coronella, Obiakor, and Mallison do not teach or suggest all claim limitations, these references do not support an obviousness rejection of claims 1-4, 14, 17-21, 23, 24, and 26.

CONCLUSION

Upon entry of this Amendment, claims 1-2, 4, 9, 12, and 15-30 will be pending in this application. Applicants submit that all claims are in condition for allowance and therefore respectfully request the Office to issue a Notice of Allowance.

This reply is being submitted as the "submission" for purposes of 37 C.F.R. § 1.114(a) and is accompanied by a petition for a five-month extension of time and the authorization to apply the required fees to Deposit Account 06-1050. If any other charges are due, please apply these charges or credits to Deposit Account 06-1050, referencing attorney docket 14875-0144US1.

Respectfully submitted,

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Janis K. Fraser, Ph.D., J.D.
Reg. No. 34,819

Fish & Richardson P.C.
Customer No. 26161
Telephone: (617) 542-5070
Facsimile: (877) 769-7945